Metabolic Syndrome and Nephrolithiasis Risk: Should the Medical Management of Nephrolithiasis Include the Treatment of Metabolic Syndrome?

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This article reviews the relationship between metabolic syndrome (MetS) and nephrolithiasis, as well as the clinical implications for patients with this dual diagnosis. MetS, estimated to affect 25% of adults in the United States, is associated with a fivefold increase in the risk of developing diabetes, a doubling of the risk of acquiring cardiovascular disease, and an increase in overall mortality. Defined as a syndrome, MetS is recognized clinically by numerous constitutive traits, including abdominal obesity, hypertension, dyslipidemia (elevated triglycerides, low high-density lipoprotein cholesterol), and hyperglycemia. Urologic complications of MetS include a 30% higher risk of nephrolithiasis, with an increased percentage of uric acid nephrolithiasis in the setting of hyperuricemia, hyperuricosuria, low urine pH, and low urinary volume. Current American Urological Association and European Association of Urology guidelines suggest investigating the etiology of nephrolithiasis in affected individuals; however, there is no specific goal of treating MetS as part of the medical management. Weight loss and exercise, the main lifestyle treatments of MetS, counter abdominal obesity and insulin resistance and reduce the incidence of cardiovascular events and the development of diabetes. These recommendations may offer a beneficial adjunctive treatment option for nephrolithiasis complicated by MetS. Although definitive therapeutic recommendations must await further studies, it seems both reasonable and justifiable for the urologist, as part of a multidisciplinary team, to recommend these important lifestyle changes to patients with both conditions. These recommendations should accompany the currently accepted management of nephrolithiasis.

[Rev Urol. 2015;17(3):117-128 doi: 10.3909/riu0650]

KEY WORDS

Nephrolithiasis • Metabolic syndrome • Uric acid nephrolithiasis

Metabolic syndrome (MetS), as defined by the National Cholesterol Education Program and the Adult Treatment Panel III in 2001 (and updated in 2005), represents a growing medical problem affecting more than 22% of US adults.[1-4] It is associated with an almost fivefold increase in the risk of developing diabetes and a doubling of the risk of acquiring cardiovascular disease.[5] MetS is a clinical disorder defined by the presence of at least three of the following criteria: central obesity (abdominal girth > 102 cm [40 in] men and > 88 cm [35 in] women), low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men and < 50 mg/dL in women), hypertriglyceridemia (> 150 mg/dL), hypertension (blood pressure > 130/85 mm Hg), and elevated fasting glucose (> 100 mg/dL).[2,4] The development of MetS appears to result from a complex interaction of genetics, phenotypic visceral fat accumulation (central obesity), insulin resistance, and sedentary behavior.[5,6] Beyond cardiometabolic risks, MetS has a wide range of long-term complications, including nonalcoholic fatty liver disease, polycystic ovarian syndrome, obstructive sleep apnea, hypogonadism, lipodystrophy, microvascular disease, and chronic renal disease.[6] An important urologic complication of MetS, not routinely cited, is nephrolithiasis.[6-8]

Nephrolithiasis continues to be a major cause of morbidity and healthcare spending.[9] A history of kidney stones is approximately twice as common in individuals with three criteria for MetS and three times as common in those with five criteria for MetS, as compared with those with none.[10] These trends were confirmed in a large-scale, nationwide study of 30,448 Japanese patients with urolithiasis, who demonstrated that MetS was associated with a significantly increased risk of hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia, independent of age and sex.[11] Additionally, patients with a history of nephrolithiasis are significantly more likely to have multiple risk factors for cardiovascular disease, premature atherosclerosis, and cardiovascular events.[10,12,13] It is unknown whether this is primarily a reflection of factors associated with nephrolithiasis, such as obesity, hypertension, or glucose intolerance/diabetes, or due to components of MetS, such as insulin resistance.[14] The current American Urological Association (AUA) guidelines on the medical management of kidney stones suggests a need for future research on advising patients to exercise and lose weight, but does not make definitive recommendations on these lifestyle changes.[15]

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Risk of Nephrolithiasis

Obesity

The prevalence of nephrolithiasis in the United States is 8.8%, affecting 1 of 11 individuals, with a significantly growing incidence.[16] Diabetes, obesity, hypertension, and MetS are interrelated clinical problems that have all individually been associated with an increased risk of nephrolithiasis.[9,17-22] Obesity has been considered a major contributor to the increased frequency of nephrolithiasis seen in recent years.[9,23,24] Obesity may also explain the apparent change in the predominance of nephrolithiasis in men, as there is an increasing frequency of kidney stones in obese women.[9,23,24] Supporting the association of obesity with nephrolithiasis is the finding of a parallel increase of both disorders observed in a national cohort study of 181,092,957 inpatients, reported by Nowfar and colleagues.[25] These authors analyzed the International Classification of Diseases, 9th Revision, diagnostic codes for renal or ureteral calculus and obesity, derived from discharges between 1998 and 2003. They demonstrated that both the incidence of obesity and nephrolithiasis increased

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significantly over this 5-year period. Other studies concur with the findings of Nowfar and colleagues,[25] demonstrating that obesity has increased from 30.5% to 35.7% between 2000 and 2010.[26] Nowfar and colleagues[25] concluded that obesity is associated with an increased risk of nephrolithiasis (all ages, both sexes), and further commented that the prevalence was disproportionately higher in obese women as compared with obese men. Although representing a large, nationwide experience and documenting a clinical correlation, the data do not demonstrate that obesity contributes directly to nephrolithiasis. Moreover, relying on diagnostic coding contributes to the study's lack of specificity regarding the absolute percentage of obese subjects, with and without MetS, and the frequency and magnitude of the individual clinical characteristics comprising the diagnostic criteria for MetS.[20]

… obesity is associated with an increased risk of nephrolithiasis …

Visceral fat accumulation (abdominal obesity), defined as a waist circumference in men ≥ 102 cm (40 in) and ≥ 88 cm (35 in) in women, is a common and frequent component of the diagnostic criteria for MetS.[4,6,20] Fujimura and associates,[27] using computed tomography-derived measure of visceral fat in 372 patients with known nephrolithiasis and 372 age-matched control subjects, found that visceral fat accumulation was a significant covariant associated with nephrolithiasis ($P < .0001$). The strength of this relationship is enhanced by the demonstration of a significant correlation in all age groups studied (< 40 y, 41-60 y, and > 60 y), although the inherent difficulties of eliminating confounders is recognized. Reviewing the association of visceral fat area, a recognized better correlate of MetS than body mass index (BMI), and uric acid nephrolithiasis, Zhou and associates[28] retrospectively reviewed data from 269 patients who underwent percutaneous nephrolithotomy. Using logistic regression analysis, they demonstrated a significantly higher mean visceral fat area in those patients with uric acid stones compared with those who did not form uric acid stones (odds ratio [OR] 3.64; 95% confidence interval [CI], 1.22–10.85; $P = .02$).[23] They also noted that hypertension was an independent risk factor for uric acid nephrolithiasis (OR 2.16; 95% CI, 1.05–4.45; $P = .04$).[28] An incidental finding was an almost threefold increase in coronary artery disease in the stone formers compared with those who did not form stones (14.3% vs 4.6%; $P = .011$).[23] Although the data from this study cannot inform us as to the specific relationship of visceral fat accumulation and hypertension to uric acid lithogenicity, the results raise consideration for studies to investigate these very points.

Diabetes

Diabetes and urolithiasis have a bidirectional relationship; that is, type 2 diabetes increases the risk of urolithiasis, and is increased in prevalence in patients with nephrolithiasis, as reported by Lieske and associates[19] (unadjusted OR for diabetes 1.29; 95% CI, 1.09–1.53).[29-31] Daudon and colleagues,[32] in their analysis of 2464 renal calculi from 272 patients with type 2 diabetes and 2192 patients without type 2 diabetes, confirmed an increased incidence of nephrolithiasis in diabetes independent of age and BMI.[32] Additionally, poor diabetes control was associated with a higher prevalence of urolithiasis, and type 2 diabetes patients had a higher prevalence of uric acid stones (35.7% vs 11.3% in patients without type 2 diabetes; $P < .0001$).[19,22,24,30,32] The presence of type 2 diabetes was identified as the strongest risk factor for the development of uric acid stones.[30] The association of MetS and diabetes with uric acid urolithiasis has been suggested to involve insulin resistance, which is the fundamental metabolic disorder in both MetS and diabetes, and is known to create defective ammoniagenesis, resulting in low urine pH, thus promoting uric acid stone formation.[16]

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Hypertension

Observed in epidemiologic studies, hypertension is associated with an increased frequency of nephrolithiasis, independent of age, body mass, or renal function.[17,18,33,34] Kohjimoto and coworkers[11] confirmed a correlation of hypertension with recurrent or multiple stones in a nationwide survey, independent of age, sex, and other MetS traits (OR 1.14; 95% CI, 1.03-1.26). Although the exact understanding of this relationship remains obscure, the association of hypertension and nephrolithiasis appears to be bidirectional[33,35]; patients with nephrolithiasis have an increased incidence of hypertension (and higher mean arterial pressures than the general population), and patients with hypertension have higher rates of kidney stone formation.[33,35]

Dyslipidemia

In a large nationwide survey of nephrolithiasis in Japan, Kohjimoto and coworkers[11] found dyslipidemia to be associated with an increased frequency of recurrent or multiple stones, independent of age, sex, or the presence of other MetS traits (OR 1.36, 95% CI, 1.22–1.52). Although they used a slightly more inclusive definition of dyslipidemia (low-density lipoprotein cholesterol $\geq$ 140 mg/dL, HDL $<$ 40 mg/dL, or triglyceride level $\geq$ 150 mg/dL), the authors also confirmed that of all of the metabolic traits reviewed, only dyslipidemia was associated, independently, with urinary lithogenic changes, including hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia.[11] These correlations of dyslipidemia raise the possible participation of a common mechanism such as insulin resistance, inflammation, and oxidative stress that may contribute to nephrolithiasis in MetS.[11]

Torricelli and coauthors[36] conducted a review of 2442 patients with nephrolithiasis who also underwent 24-hour urine studies and lipid profiles. They found that the serum concentrations of lipid components correlated with urinary changes. High total cholesterol predicted a significantly higher urinary potassium and calcium, whereas low HDL or high triglyceride levels correlated with an elevated urine sodium, oxalate, and uric acid, and a lower urine pH.[36] Furthermore, a high total cholesterol or triglyceride level was associated with a significantly higher risk of uric acid stone formation.[36] Cho and colleagues,[22] studying 712 patients with nephrolithiasis in South Korea, found significantly higher serum uric acid, lower urine pH, and a markedly increased percentage of uric acid stones in patients with MetS. In this population, triglyceride elevation and reduced HDL were associated with an increase in uric acid nephrolithiasis; however, after correction for age and sex, only triglyceride elevation maintained a statistically significant correlation.[22] Although the evidence is limited, there appears to be a definite association of dyslipidemia with urinary constituent changes that favor uric acid nephrolithiasis.

Urine Composition and pH Studies

Whether urine compositional changes predict nephrolithiasis in patients with the interrelated problems of obesity, diabetes, or MetS is unknown. Studying the relationship between BMI and urinary excretion of lithogenic factors in a cohort of 2176 stone-forming adults and 1097 nonstone-forming adults from the Health Professionals Follow-Up Study and the Nurses Health Studies I and II, Taylor and colleagues[9] and Taylor and Curhan[37] found that patients with elevated BMIs excreted more urinary oxalate ($P < .04$), uric acid ($P < .001$), sodium ($P < .001$), and phosphate ($P < .001$) than those with lower BMIs. They also found an inverse relationship between BMI and urine pH ($P < .02$).[9,37] The authors concluded that their findings of positive associations between BMI and urinary calcium excretion were due to differences in animal protein and sodium consumption.[9,37] They believe that the increased incidence of nephrolithiasis in the obese subjects is most likely due to the increased incidence of uric acid nephrolithiasis.[37] Similar observations have been made in patients with nephrolithiasis by Desai and associates[38] in a retrospective study of 256 patients (145 men and 111 women) and in a nationwide survey in Japan by Kohjimoto and colleagues,[11] as previously noted.

Desai and associates[38] found that an increased BMI raises the risk of calcium oxalate monohydrate and dihydrate, calcium phosphate, and uric acid stones with positive correlations between BMI and urine sodium and calcium oxalate. Studies of the relationship between nephrolithiasis and urine composition in patients with type 2 diabetes parallel the aforementioned findings in obese subjects. Eisner and coworkers,[39] in a retrospective analysis of 462 patients with a history of nephrolithiasis, found that patients with type 2 diabetes had a significantly higher amount of oxaluria and a significantly lower urine pH than those without type 2 diabetes. In a smaller study of patients with type 2 diabetes, Cameron and associates[40] confirmed an inverse relationship between urine pH and body weight. They concluded that the main risk contributor for nephrolithiasis in patients with type 2 diabetes is a low urine pH.[40] Using a cross-sectional study of MetS to investigate these observations further, Maalouf and colleagues[41] examined 148 adults who were known stone formers, 44 of whom were identified as having MetS. The authors found that those with MetS had a significantly lower urine pH than those without MetS, and that persistent urine acidity was the most important contributing factor to uric acid nephrolithiasis.[41,42] They concluded that an abnormally low urine pH is a feature of MetS and is associated with the degree

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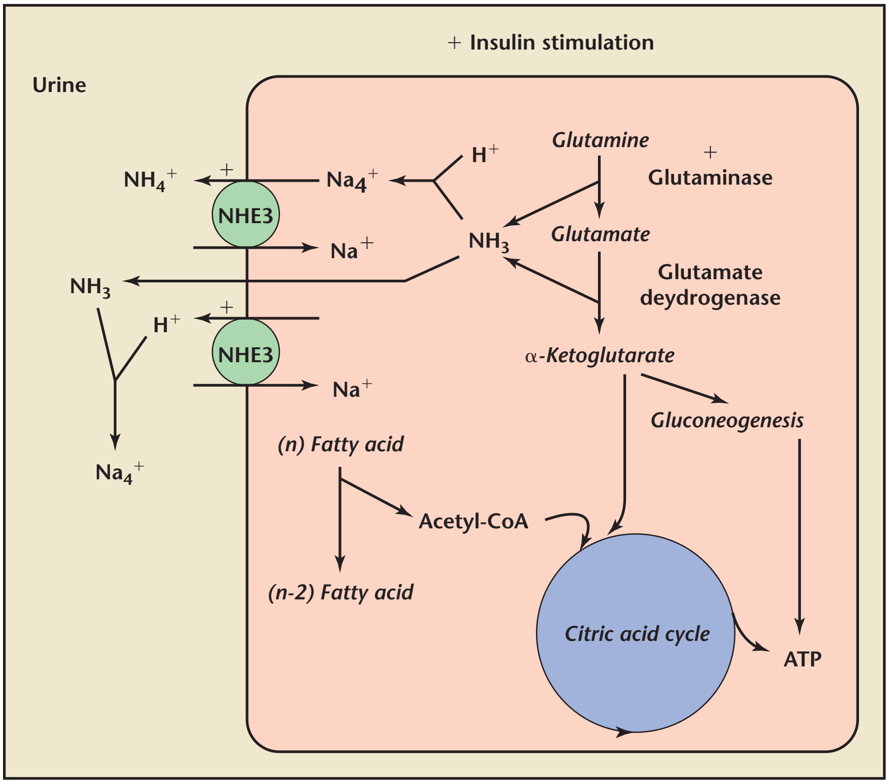


Figure 1. Potential mechanisms of ammonium generation and secretion in the proximal tubule in the setting of insulin resistance. ATP, adenosine triphosphate; CoA, coenzyme A; NHE3, sodium-hydrogen exchanger 3. Reprinted with permission from Pearle and Lotan.[53]

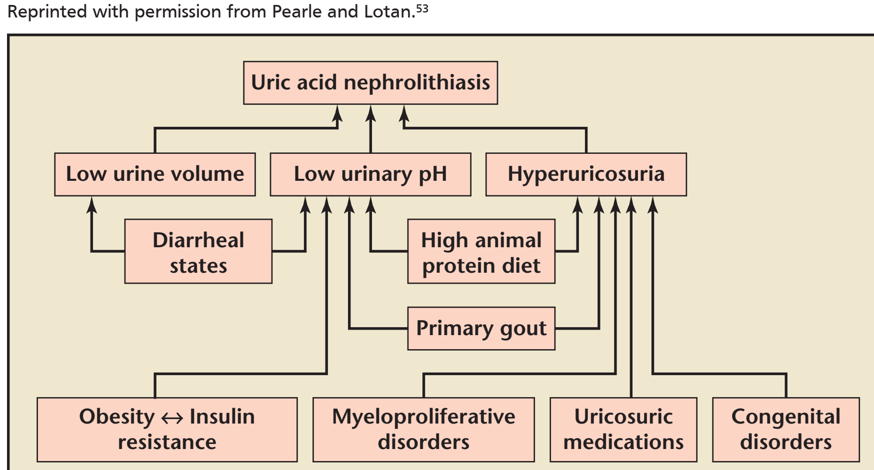
of insulin resistance.[41] The authors further uncovered a strong inverse relationship between 24-hour urine pH and the various components of MetS, which also correlate to the degree of insulin resistance.[21,41] This finding was independent of known factors to influence urinary pH (age, sex, creatinine clearance, and urine sulfate).[21,41]

Proposed Mechanism of Action

The mechanisms by which MetS may decrease urine pH include an increase in titratable acid and a decrease in base in the form of ammonium, and citrate, yielding higher hydrogen ion concentrations and a more acidic urine (Figure 1).[15,43] Several studies support the finding of low urinary pH in patients with increased body weight.[41] These authors proposed that a low urine pH results from resistance to insulin's renal actions, leading to excessive urinary acidification (Figure 1). They also found that urinary pH is inversely related to body weight among patients with nephrolithiasis, and that an increase in the incidence of uric acid stones is associated with low urine pH.[41] These authors, and others, have suggested that uric acid nephrolithiasis be considered a sequela of insulin resistance and prompt investigation for type 2 diabetes and/or the components for MetS.[22,32]

Hyperuricemia can result from increased production or decreased excretion of uric acid, or from a combination of the two processes, and may be classified as primary or secondary depending on whether the cause is innate or acquired (Figure 2).[20] Increased animal protein intake may also contribute to urine acidification, as higher ingestion and excretion of sulfur-containing acidic amino acids decrease urine pH.[44,45] Attendant increases in the ingestion and excretion of purines within animal proteins facilitates development of hyperuricosuria.[44] Uric acid, a weak acid, is more soluble in neutral or basic solutions than in acidic solutions; hence, as urine pH is lowered, the solubility of uric acid in the urine decreases and there is a greater likelihood of crystallization, especially in supersaturated solutions.[15] Coe and colleagues[43] reported that, at 37°C, pH 5.35, only one-third of the usual total urate concentration of healthy individuals is soluble, predisposing to precipitation of uric acid crystals and calculi. They concur with others that the low urine pH, as a consequence of reduced ammonia excretion, is a concomitant of insulin resistance,

Figure 2. Possible pathophysiologic pathways interrelating the metabolic syndrome and nephrolithiasis. Reprinted with permission from Pearle and Lotan.[53]



resulting from diabetes and MetS, among other causes.[43]

Oxalate, the compound most commonly combining with calcium in calcium-containing stones, is another lithogenic compound, making hyperoxaluria a common risk factor for nephrolithiasis.[9] Patients with obesity, MetS, and type 2 diabetes are predisposed to hyperoxaluria and low urine pH.[37,39-42] These factors, especially if exacerbated by dehydration, may stimulate nephrolithiasis.[42]

Intervention

It remains unknown whether specific interventions exist that can reduce the increased risk of nephrolithiasis, and uric acid nephrolithiasis specifically, in patients with hypertension, obesity, diabetes, and MetS—all insulin-resistant states.[28] Data from a basic research model suggest that it can. A study utilizing a rat model was performed by Sasaki and associates[46] in order to examine the effect of dietary calorie restriction and/or exercise on urinary stone formation. Weight loss intervention, in this study, reduced the risk of both uric acid and calcium oxalate nephrolithiasis, by improving low urine pH and increasing urinary citrate excretion.[46] This study provides the first theoretical evidence, albeit in a rat model, suggesting that weight loss and/or an exercise intervention program may reduce nephrolithiasis. Although this result cannot be extrapolated to humans, it is an intriguing finding that deserves serious consideration and future study.[24,25]

Concurrently with the increases of obesity, there has been an increase in the number of bariatric procedures performed.[47] These procedures cause a significant decrease in weight loss; however, there is a well-known causal relationship of nonanatomic procedures (jejunoileal bypass) and nephrolithiasis due to the malabsorptive state created.[47,48] Recent trends have demonstrated an increase in the utilization of anatomic or restrictive procedures that obtain similar weight loss and health outcomes, without creating as significant malabsorptive states.[47,48] One study in particular retrospectively analyzed the rate of nephrolithiasis after 332 restrictive bariatric procedures (gastric banding and sleeve gastrectomy), and found that those patients after restrictive procedures have a low incidence of nephrolithiasis.[49] Unfortunately, Chen and coworkers[49] were not able to compare these rates before and after surgery. Understanding of patients' nephrolithiasis risks prior to, during, and after weight loss intervention is paramount to prevention of stone recurrence.

Discussion

Urologic management of nephrolithiasis promotes general healthy lifestyle changes to reduce the risk of recurrent episodes. The speedy recovery from clinical episodes, and the identification of any systemic conditions that may have predisposed the patient to the disease process, are also important goals. The foundation for the AUA guidelines comes from the Agency for Healthcare Research and Quality's systematic review entitled *Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventative Medical Strategies*.[15,50] Unfortunately, the relative infrequency of acute nephrolithic events has made the study of preventative and therapeutic measures difficult, and there is limited available quality evidence upon which to base definitive guidelines.[15] Diet and lifestyle changes are recognized as effective tools for reducing the formation of nephrocalculi, although the magnitude of benefit has not been directly compared with pharmacologic therapy.[15] In view of this, recommendations remain inclusive of both diet therapy and pharmacotherapy in most clinical settings (Table 1).

With regard to uric acid nephrolithiasis specifically, medical treatment has been directed at reducing and/or reversing processes pivotal in creating the conditions that lead to urolithiasis (low urinary pH, hyperuricosuria, and low urinary volume).[51] Therapeutic measures include increasing urine flow and urine pH to between 6.0 and 6.5 with potassium citrate (30-60 mEq daily in divided doses), as well as the possible addition of allopurinol or febuxostat in patients with urine pH $>$ 6.0 and increased cell turnover or recalcitrant stone formation.[15,50,52] This may also be of benefit to patients with calcium oxalate nephrolithiasis, as uric acid crystals can serve as the catalyst in heterogeneous nucleation with calcium oxalate crystals.[53] Additional pharmacologic recommendations are summarized in Table 2. Although the AUA guidelines make dietary recommendations dependent on stone type and metabolic derangements, they do not include weight loss or exercise as a possible preventative and treatment strategy for recurrent nephrolithiasis.[15]

The profound escalation in the incidence and prevalence of obesity, hypertension, diabetes, and MetS, all insulin-resistant states, appears to be associated with an accompanying increase in the incidence of nephrolithiasis. The provocation of hyperuricemia, hyperuricosuria, and lowered urine pH, driven in part by insulin resistance and higher intakes of organic acids in the form of animal proteins and purine-containing compounds, seems to be facilitating these unfortunate trends.

TABLE 1

AUA Guideline Statements on the Medical Management of Kidney Stones: Diet Therapies

Diet Therapies
Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5 L/d (Standard; Evidence strength: Grade B)
Clinicians should counsel patients with calcium stones and relatively high urinary calcium to limit sodium intake and consume 1000-1200 mg/d of dietary calcium (Standard; Evidence strength: Grade B)
Clinicians should counsel patients with calcium oxalate stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal calcium consumption (Expert opinion)
Clinicians should encourage patients with calcium stones and relatively low urinary citrate levels to increase their intake of fruits and vegetables and limit nondairy animal protein (Expert opinion)
Clinicians should counsel patients with uric acid stones or calcium stones and relatively high uric acid levels to limit intake of nondairy animal protein (Expert opinion)
Clinicians should counsel patients with cysteine stones to limit sodium and protein intake (Expert opinion)
Pharmacologic Therapies
Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium levels and recurrent calcium stones (Standard; Evidence strength: Grade B)
Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate levels (Standard; Evidence strength: Grade B)
Clinicians should offer allopurinol to patients with recurrent calcium oxalate stones who have hyperuricosuria and normal urinary calcium levels (Standard; Evidence strength: Grade B)
Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists (Standard; Evidence strength: Grade B)
Clinicians should offer potassium citrate to patients with uric acid and cysteine stones to raise urinary pH to an optimal level (Expert opinion)
Clinicians should not routinely offer allopurinol as a first-line therapy to patients with uric acid stones (Expert opinion)
Clinicians should offer cysteine-binding thiol drugs, such as α-mercaptopropionylglycine (tiopronin), to patients with cysteine stones who are unresponsive to dietary modifications and urinary alkalinization, or have large recurrent stone burdens (Expert opinion)
Clinicians may offer acetohydroxamic acid to patients with residual or recurrent struvite stones only after surgical options have been exhausted (Standard; Evidence strength: Grade B)

AUA, American Urological Association. Adapted from Pearle MS et al.[15]

The cost estimates of treating nephrolithiasis extend from $3.8 billion to beyond $10 billion per year.[26,54] It is estimated that this annual cost may increase to greater than $15 billion by 2030.[26,55] This anticipated increase in the cost of nephrolithiasis is exacerbated, in part, by the progressive increases in rates of obesity and diabetes, and economic factors including inflation and the overall cost of healthcare delivery.[26] Turney and Reynard[55] offer cogent arguments about these trends, and discuss the importance of a continued focus on prevention of nephrolithiasis as opposed to a monolithic treatment approach.

The management of nephrolithiasis associated with MetS and diabetes has been similar to the general management of nephrolithiasis.[6] Both weight loss and exercise are associated with reductions in insulin resistance. Whether recommendations for an aggressive approach to lifestyle changes,

TABLE 2

Urolithiasis Pharmacotherapy

Agent	MOA	Evidence Strength	Pathophysiologic Effect	Dosing
Thiazides/thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, indapamide)	Increase calcium reabsorption in distal renal tubule and through extracellular volume depletion in the proximal tubule	Grade B	Decrease in urinary calcium	HCTZ, 25 mg BID; chlorthalidone 25-50 mg/d; indapamide 1.25-2.5 mg/d
Potassium citrate	Binds to ionized calcium; inhibits calcium oxalate and calcium phosphate crystallization	Grade B	Decrease in urinary ionized calcium; increase in urinary citrate and pH	15-20 mEq BID
Allopurinol	Inhibits xanthine oxidase	Grade B	Decrease in serum and urinary uric acid	300 mg/d
Acetohydroxamic acid	Inhibits urease		Decrease in urine pH and urinary urea	250 mg TID
α-mercaptopropionyl glycine	Disulfide exchange		Decrease in urinary cystine	Titrate to effect and absence of side effects

BID, twice daily; HCTZ, hydrochlorothiazide; MOA, mechanism of action; TID, three times daily.
Data from Pearle MS et al.[15]

to effect meaningful weight loss through calorie restriction, and increased calorie expenditure through exercise, might reduce the frequency of nephrolithiasis and promote more effective treatment of established cases has not been adequately tested. These recommendations, however, are associated with reductions in cardiometabolic complications of MetS and diabetes, and may very well be associated with favorable effects on the processes promoting nephrolithiasis. Recently, it has been proposed that diet and exercise should be encouraged for patients with MetS in order to prevent nephrolithiasis.[56] It seems appropriate, perhaps even compelling, for the urologist to emphasize these therapeutic lifestyle changes, simultaneous with the current treatments for nephrolithiasis, even before specific effects regarding the complications of nephrolithiasis are known. Albeit a consensus position, we concur with the multidisciplinary team approach, including the urologist, nephrologist, primary care provider, and dietitian, as suggested by Monga and colleagues,[56] when treating a patient with MetS and nephrolithiasis. We agree with the suggestion of Daudon and associates[32] to investigate for type 2 diabetes and components of MetS whenever presented with a patient with uric acid nephrolithiasis, even if this approach lacks strong direction from randomized, controlled, definitive studies.[19]

Conclusions

Patients with MetS have an increased risk of nephrolithiasis, which includes a heightened prevalence of uric acid nephrolithiasis, promoted by low urinary pH, hyperuricosuria, and low urinary volume. Weight loss and exercise, the main lifestyle treatments of MetS, counter abdominal obesity and the resulting insulin resistance, which appears to play an important role in the pathogenesis of low urine pH and uric acid precipitation. These measures also reduce cardiovascular events and the development of diabetes. Recommendations to improve lifestyle, through weight loss and exercise, will likely offer a beneficial adjunctive treatment option for nephrolithiasis complicated by MetS. Although definitive therapeutic recommendations must await further study, it seems both reasonable and justifiable for the urologist, working within a multidisciplinary team, to recommend these important lifestyle changes

TABLE 3

Articles Examined

Author	Study Design	N	Conclusions
Nowfar S et al[25]	Retrospective	NSQIP Database	Obesity is significantly associated with an increased prevalence of urinary stones with a stronger relationship in women
Scales CD Jr et al[16]	Retrospective (NSQIP)	NSQIP Database	Increased stone disease in women, possibly representing a change in the prevalence by sex from a 1.7:1 to 1.3:1 male:female ratio
Lieske JC et al[19]	Retrospective	260	Diabetes, obesity, and hypertension are associated with nephrolithiasis, and diabetes may be a factor in the development of uric acid stones
Weinberg AE et al[30]	Cross- sectional analysis	NHANES Database	Patients with type 2 diabetes: more severe disease is associated with a heightened risk of kidney stones
Cho ST et al[22]	Cohort	712	MetS is associated with a significantly increased risk of uric acid calculi development, especially in those with impaired fasting glucose and hypertriglyceridemia
Meydan N et al[31]	Cohort	397	Diabetes is a risk factor for the development of nephrolithiasis
Inci M et al[24]	Cohort	49	Elevated BMI, hypercholesterolemia, and hyperlipidemia may be associated with different types of urinary stone formation
Rendina D et al[7]	Meta-analysis	5 cross-sectional studies	MetS associated with statistically significant increase in nephrolithiasis prevalence in both adult and pediatric patients
Borghi L et al[17]	Cohort	132	A significant number of hypertensive patients have a greater risk of renal stone formation, which is compounded by higher BMI, with higher oxaluria and calciuria, as well as supersaturation of calcium oxalate and uric acid
Desai A et al[38]	Retrospective	256	Increased risk of uric acid stones with increasing BMI
Tracy CR et al[44]	3-phase randomized, crossover metabolic study	15	Animal protein consumption is associated with increased serum and urine uric acid in healthy individuals with stone-forming propensity and is higher for beef compared with fish or chicken
Kohjimoto Y et al.[11]	Cross-sectional analysis	30,448	MetS traits are associated with increased severity of kidney stone disease and elevated urinary excretions of calcium, uric acid, and oxalate (men > women)
Fujimura M et al[27]	Retrospective	744	Visceral fat accumulation significantly correlated with incidence of stone formation in men
Strazzullo P et al[18]	Cohort	381	A history of nephrolithiasis results in an increased risk of developing future hypertension
Cappuccio FP et al[33]	Cohort	503	Hypertension in middle-aged men is a significant predictor of kidney stone disease rather than a consequence of renal damage caused by the kidney stones

TABLE 3

Articles Examined (*Continued*)

Author	Study Design	N	Conclusions
Tang J et al[34]	Retrospective	NHANES Database	Although there is increased risk of all-cause and cardiovascular mortality in kidney stone formers, this is likely a reflection of unique demographics and associated comorbidities with no independent association
Zhou T et al[28]	Retrospective	269	Uric acid stone formers show a significantly higher hypertension rate and mean visceral fat area, which were independent risk factors for uric acid urolithiasis
Reddy ST et al[45]	Retrospective	Pediatric population	No link between pediatric urolithiasis and obesity
Cameron MA et al[40]	Cross-sectional analysis	91	The main risk factor for uric acid nephrolithiasis in patients with type 2 diabetes is a low urine pH
Daudon M et al[32]	Cohort	272	Strong association between type 2 diabetes and uric acid stone formation
Maalouf NM et al[41]	Cross-sectional analysis	148	Acidic urine is a feature of the metabolic syndrome and is associated with the degree of insulin resistance
Eisner BH et al[57]	Retrospective	462	Patients with nephrolithiasis and type 2 diabetes excrete significantly higher amounts of urinary oxalate and have lower urine pH than those without type 2 diabetes
Taylor EN et al[37]	Meta-analysis	—	Positive associations between BMI and urinary calcium excretion are likely due to differences in animal protein and sodium intake
Shekarriz B et al[42]	Review	—	Acidic urine is a prerequisite for uric acid stone formation and growth; medical management with urinary alkalization for stone dissolution and prevention of recurrence is effective and should be the cornerstone of treatment
Torricelli FC et al[36]	Retrospective	2442	A link exists between dyslipidemia and kidney stone risk, independent of other components of metabolic syndrome
Torricelli FC et al[58]	Retrospective	214	Dietary modification decreases nephrolithiasis incidence in obese and super obese patients equally to the effect seen in nonobese patients
Sasaki Y et al[46]	Review: 13 studies	—	Weight loss intervention reduces the risk of uric acid stone formation by improving low urine pH and calcium oxalate stone formation by increasing urinary citrate excretion

BMI, body mass index; MetS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey; NSQIP, National Surgical Quality Improvement Program.

to the patient with the dual diagnoses of nephrolithiasis and MetS, along with currently accepted empirical treatments of nephrolithiasis. ■

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MAIN POINTS

- Metabolic syndrome (MetS), defined by the presence of at least three of the following criteria: central obesity, and low high-density lipoprotein cholesterol, hypertriglyceridemia, hypertension, and elevated fasting glucose, affects more than 22% of US adults. It is associated with an almost fivefold increase in the risk of developing diabetes and a doubling of the risk of acquiring cardiovascular disease. Beyond cardiometabolic risks, MetS has a wide range of long-term complications, including nonalcoholic fatty liver disease, polycystic ovarian syndrome, obstructive sleep apnea, hypogonadism, lipodystrophy, microvascular disease, and chronic renal disease. An important urologic complication of MetS, not routinely cited, is nephrolithiasis.
- Nephrolithiasis continues to be a major cause of morbidity and healthcare spending. A history of kidney stones is approximately twice as common in individuals with three criteria for MetS and three times as common in those with five criteria for MetS, as compared with those with none. Patients with a history of nephrolithiasis are significantly more likely to have multiple risk factors for cardiovascular disease, premature atherosclerosis, and cardiovascular events. It is unknown whether this is primarily a reflection of factors associated with nephrolithiasis, such as obesity, hypertension, or glucose intolerance/diabetes, or due to components of MetS, such as insulin resistance.
- Poor diabetes control was associated with a higher prevalence of urolithiasis, and type 2 diabetes was associated with a higher prevalence of uric acid stones. The presence of type 2 diabetes was identified as the strongest risk factor for the development of uric acid stones. The association of MetS and diabetes with uric acid urolithiasis has been suggested to involve insulin resistance, which is the fundamental metabolic disorder in both MetS and diabetes, and is known to create defective ammoniagenesis, resulting in low urine pH, thus promoting uric acid stone formation.
- Diet and lifestyle changes are recognized as effective tools for reducing the formation of nephrocalculi, although the magnitude of benefit has not been directly compared with pharmacologic therapy. In view of this, recommendations remain inclusive of both diet therapy and pharmacotherapy in most clinical settings. Recommendations to improve lifestyle, through weight loss and exercise, will likely offer a beneficial adjunctive treatment option for nephrolithiasis complicated by MetS.

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